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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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DEWITT ROSS & STEVENS S.C.
8000 EXCELSIOR DR
SUITE 401
MADISON, WI 53717-1914

EXAMINER	
GUO, LYNDA T	

ART UNIT	PAPER NUMBER
1651	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/871,424	Applicant(s) GOUELI ET AL.	
	Examiner Lynda T Guo	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *1-30 and 47-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

The Restriction Response/Preliminary Amendment (Paper No. 11) received on 27 November 2002 has been entered.

Claims 1-53 of the present Application are pending. Claims 31-46 are examined in this Office Action.

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 31-46 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that:

a) In regards to Invention Groups I, II, and III, Applicant argues that no reason was given to support the position that the inventions are patentably distinct. Additionally, Applicant argues that the search for the three Groups is not burdensome because they are all methods for assaying kinases or phosphatases and thus share the same classification.

b) In regards to Invention Groups I-III and IV, Applicant argues that, "The Examiner has provided no indication as to how performing the process 'by hand' is materially different from using the claimed kit to perform the process, in which case the process is arguably carried 'by hand' in any event." Applicant further argues that the kit, as claimed, "is specifically designed to carry out the process of Groups I, II, and III."

c) In regards to the election of species, Applicant argues that no reasons were given to show how the species identified by the Examiner are patentably distinct.

This is not found persuasive because:

a) In regards to Invention Groups I, II, and III, although each claimed method is for assaying kinases and phosphatases, the steps and the reagents and materials required for each method are different, as evidenced by the examples given in the previous Office Action (Paper No. 9). More specifically, according to the method of Group I, the enzyme and substrate are first reacted and then the product is fixed to the matrix. According to the method of Group II, a binding moiety is included, this binding moiety is lacking in the methods of Group I and III. As for Group III, the substrate is first bound to a matrix and then reacted with the enzyme. This is clearly different from the other two methods in which only the product is bound after the enzymatic reaction took place. The three methods, therefore, carry individual patentability and are thus properly restrictable.

b) In regards to Invention Groups I-III and IV, the kit was wrongly designated as an apparatus. The kit rightly qualifies as a product. In this regard, the methods of Inventions I-III and the kit (product) of Invention IV are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the kit can be used in materially different processes. Examples of the different processes are the three methods claimed in Inventions I-III. The restriction between the kit and the methods are therefore proper.

c) In regards to the election of species, this election is required only if invention Group II was elected. Notice Claims 15-18 were recited in the species election requirement. (The Examiner apologizes for not clarifying this in the prior office action.) Since Applicant elected invention

Group III, the species election is not necessary and therefore not taken into consideration for the instant Office Action.

The requirement is still deemed proper and is therefore made **FINAL**.

2. Claims 1-30 and 47-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Specification

3. The disclosure is objected to because of the following informalities: on page 9, line 22, "When the reaction was been performed..." is grammatically incorrect.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 recites the limitation "the enzyme is contacted with a binding matrix". There is insufficient antecedent basis for this limitation in the claim because in Claim 31, it is the enzyme **substrate** that is bound to the matrix, not the enzyme itself.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 31 is rejected under 35 U.S.C. 102(b) as being anticipated by Toomik et al. (Peptide Research, 1996).

Claim 31 is drawn to an assay method for enzymes classified in EC 2.7.1, EC 3.1.3, or EC 3.1.4. The method comprises fixing a substrate for the enzyme to a binding matrix, then reacting the substrate to the enzyme, and then analyzing the product that is fixed to the matrix.

Toomik et al. discloses that membrane-bound peptides can serve as protein kinase substrates (Abstract, lines 6-10). In this disclosure, Toomik et al. fixes the peptides to a cellulose membrane by synthesizing the peptide onto the membrane. These membrane-bound substrates were then reacted with kinases. The phosphorylated products, still bound to the membrane, were then detected and analyzed. In addition to kinases, the phosphorylated, membrane-bound peptides were reacted with phosphatases to dephosphorylate the peptides. (See page 7, left column, last paragraph; middle column, last paragraph; and right column, last two paragraphs.) The method as claimed in Claim 31 is clearly encompassed by the disclosure of Toomik et al. The Claim is therefore rejected.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 32-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toomik et al. (Peptide Research, 1996) in view of Promega Technical Bulletin No. 547, in further view of Sartobind® product brochure.

Claims 32-43 are dependent on Claim 31. Specifically, Claims 32-37 are directed to the assay method as applied to kinases, especially those classified in EC 2.7.1.67, EC 2.7.1.68, or EC 2.7.1.137, whose substrate is a phosphoinositide. Additional limitations include the use of an aldehyde-activated support, especially an aldehyde-activated regenerated cellulose support, as the matrix and the use of labeled phosphate groups, especially ^{32}P-labeled phosphate groups, in the reaction. The analysis is carried out in a scintillation counter or phosphorimager. Claims 38-

43 share the same limitations as Claims 32-37 except that the enzymes as phosphatases classified in EC 3.1.3.27, EC 3.1.3.36, EC 3.1.3.64, EC 3.1.3.67, EC 3.1.4.10, and EC 3.1.4.11.

As recited supra, Toomik et al. discloses the use of cellulose membrane-bound peptides as substrates in assays for kinases and phosphatases. In the assay mixture, ^{32}P-ATP serves as the phosphate group. After the reaction, products were measured via autoradiography or Cerenkov counting. (See page 7, middle column, last paragraph and right column, last 2 paragraphs, and page 11, left column, lines 1-3.) Toomik et al. do not expressly disclose: 1) the use of the particular enzymes claimed in the present invention; 2) analyzing the results with a scintillation counter or phosphorimager; or 3) the use of aldehyde-activated support. However, kinases by nature phosphorylate their substrates and phosphatases dephosphorylate their substrates. One kinase or phosphatase is interchangeable for another because the reaction mechanisms of all kinases are the same and the reaction mechanisms for all phosphatases are the same. In regards to the substrate used, each enzyme has its own specific substrate; therefore, depending on the enzyme of interest assayed, the substrate will be selected accordingly. Applicant also discloses in the instant application that the instant method can be used to assay for any kinase within EC 2.7.1 and any phosphatase in EC 3.1.3 and EC 3.1.4, without limitation (See page 16, lines 11-13 and page 18, lines 30-32). In regards to analysis of the assay via scintillation counting or phosphorimaging, the Promega bulletin teaches that when radioisotopes are used (in this instance, for a kinase assay), analysis can be done via a scintillation counter or a phosphorimaging system (page 3, last paragraph, lines 2-4 and page 6, Note No. 6). In regards to the specific matrix used (i.e. the aldehyde-activated support), the technical bulletin from Promega teaches that, "It is frequently desirable in molecular biology and enzymatic analysis to

separate a specific substrate from other compounds in a reaction mix. This separation is usually accomplished using a solid matrix that selectively binds the substrate." (Page 3, lines 1-3 of section A.) The Sartobind® Aldehyde Membranes product brochure discloses that this membrane is used for coupling (i.e. binding) amine containing ligands (i.e. substrates) like proteins and peptides (left column, first paragraph). (NOTE: The Sartobind® Aldehyde Membranes have been commercially available since 1996, according to Sartorius Corporation, USA.) In summary, one of ordinary skill in the art, at the time the invention was made, would have been motivated to modify the method as taught by Toomik et al. by tailoring the binding matrix to suit the substrates and enzymes that one desires to assay because depending on the enzyme being assayed, the substrate will be selected accordingly, and depending on the substrate selected, the membrane that can bind specifically to the substrate will be chosen accordingly. In the instant application, the aldehyde membrane would have been preferable because the substrate is a phosphatidylinositol peptide, which would be selectively bound to the aldehyde membrane via the amino group of the peptide.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Toomik et al. (Peptide Research, 1996) as applied to Claim 31 above, and further in view of Shultz et al. (USPN 5,580,747).

As recited above, Toomik et al. discloses the use of cellulose membrane-bound peptides as substrates in assays for kinases and phosphatases. The method, as disclosed by Toomik et al. has the advantage of being rapid and inexpensive (Abstract, lines 25-27), but Toomik et al. does not teach that the substrate is contained in a cell lysate and it is the cell lysate that is contacted with the matrix. However, Shultz et al. teaches the use of "crude extracts", defined as "an extract

from an entire organism or tissue made by lysis of the tissue or organism", in a kinase assay wherein the crude extract is reacted with the kinase enzyme and the activity of the enzyme was detectable. (See Column 10, lines 57-59 and Column 22, lines 23-26). One of ordinary skill in the art would have been motivated to modify the method as taught by Toomik et al. by using a crude extract (i.e. a cell lysate) because, in addition to the speed and inexpensiveness of the method, Toomik et al. has shown that enzymes can act on bound substrates and Shultz et al. has shown that the enzyme is not inactivated in a mixture with cell lysate components. Absent unexpected results, the method, as claimed is therefore obvious.

Claims 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toomik et al. as applied to claim 31 above, and further in view of Alexis Biochemicals Product Data Sheet and Promega Technical Bulletin No. 547.

As recited above, Toomik et al. discloses the use of cellulose membrane-bound peptides as substrates in assays for kinases and phosphatases. Toomik et al. also teaches that an advantage of their disclosed method is the "ease in separating products from reactants (Page 11, left column, third paragraph, lines 5-8). Toomik et al. does not teach: 1) that the substrate is contained in an organic-phase solution and it is the organic-phase solution that is contacted with the matrix; and 2) contacting the substrate to the matrix in the absence of drying the substrate or extracting the substrate from an organic phase prior to contacting it to the matrix. However, it is well known in the art that peptides, particularly those with long alkyl chains, are more soluble in organic solvents. For example, the purified substrate PI4,5P2 (the substrate recited in Example 1 of the instant specification on page 24) is soluble in DMSO, as disclosed in the "Solubility" heading on product data sheet from Alexis Biochemicals (the company that Applicant obtained

purified substrates from, as recited on page 8 of the instant specification). Additionally, as taught by the Promega bulletin, the use of a solid matrix that selectively binds the substrate is useful to separate the substrate from other compounds in a reaction mixture (page 3, lines 1-3 of Background section). Therefore, it would have been obvious to one of ordinary skill in the art to modify the method of Toomik et al. by applying an already synthesized and purified substrate that is contained in an organic-phase solution to the matrix because: 1) the substrate remains dissolved for easier binding to the matrix; and 2) drying the substrate or extracting the substrate from an organic phase is obviated since the matrix will inevitably separate the substrate, as well as the product, from all other compounds once the substrate binds to the matrix. The invention as claimed is therefore rendered obvious, absent any unexpected results.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Gallis (USPN 4,923,802) discloses an assay for protein kinase C in which the radioactively phosphorylated product is bound to a phosphocellulose filter prior to measurement in a scintillation counter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynda T Guo whose telephone number is (703) 605-1200. The examiner can normally be reached on Tue - Fri and alternate Mondays (9:00am - 7:00pm).
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on (703) 308-4743. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Lynda T Guo
Patent Examiner
January 29, 2003

Jon P. Weber, Ph.D.
Primary Examiner